CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS (DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM: 2 CHEMICALS IDENTIFIED BY US EPA

PACKAGE 15:
December 24, 1998

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The 2 chemicals listed in the table below may meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

US EPA has been identified as an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)) and has identified the chemicals in the table below as causing developmental or reproductive toxicity. This was done by that Agency in implementing its Toxics Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 [EPCRA]). On the basis of identifying chemicals which caused reproductive, developmental and/or other toxicities the US EPA added a number of chemicals to the TRI list. The US EPA published its toxicity findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect…" (*Federal Register* **59:**1790).

OEHHA has found that the chemicals in the table below have been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306[d]) because the chemicals have "been identified as causing … reproductive toxicity by the authoritative body" (*i.e.*, US EPA) "in a document that indicates that such identification is a final action" (*i.e.*, the TRI *Final Rule* [*Federal Register* **59:**61432]) and have "been included on a list of chemicals causing … reproductive toxicity issued by the authoritative body" "and the document specifically and accurately identifies the chemical" and has been "published by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306[g]) appear to have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the documents and reports cited by US EPA in making their finding that the specified chemicals cause reproductive toxicity. In some cases,

OEHHA consulted additional sources of information on the specific studies cited by US EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by US EPA; OEHHA did not review additional studies not relied on by US EPA.

A major source of information used by the US EPA was the "Tox-Oneliner" database maintained by US EPA's Office of Pesticide Programs (OPP). This database consists of brief summaries of (usually unpublished) data submitted to the Agency in compliance with regulatory requirements. Many database entries include a notation of "core grade" – a system formerly used by US EPA to indicate the extent to which a study conformed to published test guidelines (US EPA 1983a and 1983b). Under this scheme, a "core grade guideline" study was considered to meet all guideline requirements; a "core grade minimum" study was considered sufficient for risk assessment; and a "core grade supplementary study" was considered to provide useful supplementary information, but not to be suitable for risk assessment on its own.

Chemical	CAS No.	Endpoint	Pesticide status or usage
Imazalil	35554-44-0	developmental toxicity	Registered in CA
Propargite	2312-35-8	developmental toxicity	Registered in CA

Studies cited by US EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306[g]). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group. Where NOELs (no-observed-effect-level), LOELs (lowest-observed-effect-level), or LELs (lowest-effect-level) are included in the study descriptions below, they are quoted directly from the cited references.

Imazalil (CAS No. 35554-44-0)

Developmental toxicity **was evidenced by decreased litter size and increased dead fetuses in rats, and reduced fetal viability in rabbits.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "...there is sufficient evidence for listing imazalil on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "In a rat teratology study, increased maternal mortality, decreased litter size, and increased number of dead fetuses were observed in animals administered 40 mg/kg/day (LOEL). The NOEL was 10 mg/kg/day (11 [US EPA, 1993c]). The study was classified Core Minimum. Stillbirths and altered live birth index were observed in rats orally administered 80 mg/kg/day days 16 through 22 of gestation and 21 days post gestation (9 [RTECS, 1993]). Altered lactation index was observed in rats orally administered 20 mg/kg/day days 16 though 22 of gestation and 21 days post gestation (9 [RTECS, 1993]). Post implantation loss was observed in rabbits orally administered 0.63 mg/kg/day on days 6 through 18 of gestation (9 [RTECS, 1993]). Altered viability index was observed in rabbits orally administered 2.5 mg/kg/day on days 6 through 18 of gestation (9 [RTECS, 1993]). No other studies showing developmental toxicity effects for imazalil are available."

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study. Core grade 'minimum' (US EPA, 1993c).
   Study b) rat developmental toxicity study. Data from this study cannot be considered suitable for hazard assessment as: 1) Maternal toxicity at the high dose of 80 mg/kg/day was extreme (25% mortality), confounding interpretation of the increased stillbirth weight observed at that dose, and 2) The only effect documented at the middle dose of 20 mg/kg/day was decreased survival at weaning, an effect which cannot be attributed to prenatal exposure alone (Thienpont et al., 1981).
   Study c) rabbit developmental toxicity study. The number of animals per dose group meets guideline requirements, but there were only two (rather than three) dose groups. Reporting of methods and results is so incomplete as to limit the usefulness of this study for hazard/risk assessment.
2. **Route of administration:**
   Study a) not stated, but presumably oral, due to designation as meeting guideline requirements.
   Study b) oral, diet (Thienpont et al., 1981).
   Study c) oral, gavage (Thienpont et al., 1981).

3. **The frequency and duration of exposure**:
   Study a) not stated explicitly, but Agency designation as 'core grade minimum' (sufficient for risk assessment) indicates that the study came close to, or met, test guideline requirements of daily treatment on each of gestation days 6-15 (US EPA, 1983).
   Study b) gestation days 16-22, and 21 days postnatally (Thienpont et al., 1981).
   Study c) gestation days 6-18 (Thienpont et al., 1981).
4. **The numbers of test animals:**
   Study a) not stated explicitly, but Agency designation as 'core grade minimum' (sufficient for risk assessment) indicates that the study came close to, or met, test guideline requirements of 20 pregnant animals per dose group (US EPA, 1983).
   Study b) 20 animals per group (Thienpont et al., 1981).
   Study c) 20 animals per group (Thienpont et al., 1981).
5. **The choice of species:**
   Rats and rabbits are species typically used in toxicity testing.
6. **The choice of dosage levels:**
   Study a) 0, 10, 40 mg/kg/day (and possibly one more dose level as well, as required by US EPA test guidelines).
   Study b) 0, 5, 20, and 80 mg/kg/day (Thienpont et al., 1981).
   Study c) 0, 0.63, 2.5 mg/kg/day (Thienpont et al., 1981).
7. **Maternal toxicity:**
   Study a) LEL=40 mg/kg/day, NOEL=10 mg/kg/day (based on increased maternal mortality and decreased food consumption). These values are identical to those determined for developmental toxicity, which are based on decreased litter size and increased number of dead fetuses.
   Study b) There was 25 % maternal mortality in the high-dose group given 80 mg/kg/day. Food consumption during the treatment period was also significantly reduced at this dose (Thienpont et al., 1981).
   Study c) Reduced body weight gain was observed at the low dose of 0.63 mg/kg/day, and body weight loss was observed at the high dose of 2.5 mg/kg/day.

Propargite (CAS No. 2312-35-8)

Developmental toxicity **was evidenced by adverse effects on viability, fetal weights, and ossification of skeletal elements.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing Propargite on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In the rabbit developmental toxicity study (IRIS, 1993 [US EPA, 1993d]) delayed ossification, increased resorption, decreased fetal viability and reductions in fetal body weight were noted in offspring of female rabbits exposed via oral gavage to doses $\geq$ 6 mg/kg/day (fetotoxic

LOAEL) during gestation days 6-18. The maternal LOAEL in this study was also 6 mg/kg/day and was based on body weight reductions; the NOEL for maternal and fetal toxicity was 2 mg/kg/day. These developmental effects may have been secondary to the maternal toxicity. Developmental effects (increased incidence of missing sternabrae) were also reported in offspring of rats exposed orally during gestation days 6-15; the fetotoxicity LOAEL was 25 mg/kg/day and the NOAEL was 6 mg/kg/day."

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study - Stated (US EPA, 1993d) to be core grade minimum.
   Study b) rabbit teratology study - Stated (US EPA, 1993d) to be core grade minimum.
2. **Route of administration:**
   Study a) oral gavage
   Study b) oral gavage
3. **The frequency and duration of exposure:**
   Study a) each of gestation days 6 - 15.
   Study b) each of gestation days 6 - 18.
4. **The numbers of test animals:**
   Study a) not stated explicitly, but Agency designation as 'core grade minimum' (sufficient for risk assessment) indicates that the study came close to, or met, test guideline requirements of 20 pregnant animals per dose group (US EPA, 1983).
   Study b) 17 pregnant rabbits per dose group.
5. **The choice of species:**
   Rabbits and rats are standard test species for toxicity studies.
6. **The choice of dosage levels:**
   Study a) 0, 6, 25, 105 mg/kg/day
   Study b) 0, 2, 6, 10, 18 mg/kg/day.
7. **Maternal toxicity:**
   Study a) maternal toxicity was observed only at doses higher than those associated with adverse effects on development.
   Study b) maternal and developmental toxicity were noted at the same dose levels (NOEL=2 mg/kg/day; LOEL=6 mg/kg/day).

References

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US Environmental Protection Agency (US EPA, 1993a). *Support Document for the Addition of Chemicals from Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Active Ingredients to EPCRA Section 313.* US EPA Office of Pesticide Programs, Washington, DC.

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